



Clinical trial results:

A multi-center, un-controlled, open-labeled trial of the long-term safety of Velmanase Alfa aftercare treatment of subjects with alpha-Mannosidosis whom previously participated in velmanase alfa - trials

Summary

| | |
|--------------------------|-------------------|
| EudraCT number | 2013-000321-31 |
| Trial protocol | DK PL |
| Global end of trial date | 30 September 2022 |

Results information

| | |
|--------------------------------|--------------|
| Result version number | v1 (current) |
| This version publication date | 21 May 2023 |
| First version publication date | 21 May 2023 |

Trial information

Trial identification

| | |
|-----------------------|------------|
| Sponsor protocol code | rhLAMAN-09 |
|-----------------------|------------|

Additional study identifiers

| | |
|------------------------------------|-------------------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT01908725 |
| WHO universal trial number (UTN) | - |
| Other trial identifiers | EudraCT: 2013-000321-31 |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | Chiesi Farmaceutici S.p.A |
| Sponsor organisation address | Via Palermo 26/A, Parma, Italy, 43122 |
| Public contact | Chiesi Clinical Trial, Chiesi Farmaceutici S.p.A, 0039 05212791, clinicaltrials_info@chiesi.com |
| Scientific contact | Chiesi Clinical Trial, Chiesi Farmaceutici S.p.A, 0039 05212791, clinicaltrials_info@chiesi.com |

Notes:

Paediatric regulatory details

| | |
|--|-----|
| Is trial part of an agreed paediatric investigation plan (PIP) | No |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | Yes |

Notes:

Results analysis stage

| | |
|--|-------------------|
| Analysis stage | Final |
| Date of interim/final analysis | 21 April 2023 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 30 September 2022 |
| Global end of trial reached? | Yes |
| Global end of trial date | 30 September 2022 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

Primary objective: evaluation of safety of repeated velmanase alfa intravenous (i.v.) treatment of subjects with alpha-mannosidosis; monitoring long-term safety profile including immunogenicity (anti-immunoglobulin (Ig)G) anti-drug antibodies (ADAs)).

Secondary objectives: evaluating long-term efficacy of velmanase alfa on endurance (6-Minute Walk Test (6MWT), 3-Minute Stair Climb Test (3MSCT)), pulmonary function, serum oligosaccharides, hearing, cognitive development (Leiter International Performance Scale - Revised), motor proficiency (Bruininks-Oseretsky Test of Motor Proficiency, 2nd edition), quality of life (Childhood Health Assessment Questionnaire (CHAQ), EuroQoL-5 Dimensions 5-Levels Questionnaire), cerebrospinal fluid (CSF) and 24-hour urine oligosaccharides, central nervous system involvement (imaging and CSF biomarkers (tubulin associated unit, neurofilament light and glial fibrillary acidic proteins)), in vivo biological activity and evaluating pharmacokinetics.

Protection of trial subjects:

The trial was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines, and following all other requirements of local laws. Subjects who had enrolled in earlier velmanase alfa trials (rhLAMAN-02/-03/-04 and rhLAMAN-05) were enrolled. Adverse events (AEs) including infusion-related reactions were collected at every visit. Other safety assessments (performed as per the trial flow chart) included laboratory evaluations (haematology, biochemistry, urinalysis, coagulation tests), physical examination, recording of vital signs (systolic and diastolic blood pressure, heart rate, respiratory rate and body temperature), tests for ADAs and neutralising antibodies (every 12 weeks) and serum IgG/IgM/IgA (every 24 weeks). Electrocardiograms (ECGs) and echocardiograms were recorded at a comprehensive evaluation visit (CEV) performed by 7 subjects who had enrolled in earlier trials. At dosing visits, medical personnel continuously observed subjects until 1 hour post-infusion; observation periods were prolonged if required. Medical/surgical history was recorded at screening. Concomitant medications were collected throughout the trial. During the coronavirus disease 2019 (COVID-19) pandemic, a contingency plan was developed for protection of subjects in treatment phase and appropriate mitigation actions were adopted according to local regulations. As onsite visits were on hold, site staff performed weekly phone calls to obtain information on active subject status, AEs and concomitant medications.

Background therapy: -

Evidence for comparator: -

| | |
|---|--------------|
| Actual start date of recruitment | 10 June 2013 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|------------|
| Country: Number of subjects enrolled | Denmark: 8 |
| Worldwide total number of subjects | 8 |
| EEA total number of subjects | 8 |

Notes:

| Subjects enrolled per age group | |
|---|---|
| In utero | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |
| Newborns (0-27 days) | 0 |
| Infants and toddlers (28 days-23 months) | 0 |
| Children (2-11 years) | 3 |
| Adolescents (12-17 years) | 2 |
| Adults (18-64 years) | 3 |
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

Subjects who had completed the rhLAMAN-04 or rhLAMAN-05 trials of velmanase alfa were eligible for inclusion and 8 subjects were enrolled. Efficacy evaluations were performed in Denmark for all subjects. Infusions were performed in Denmark (for subjects based in Norway and the 1 subject based in the UK) and Poland (for subjects based in Poland).

Pre-assignment

Screening details:

An informed consent from subjects/their legally authorised guardians was obtained prior to any trial-related procedures. Inclusion/exclusion criteria were checked, medical/surgical history and concomitant medications and illnesses were collected, demographics were recorded and a serum pregnancy test was performed as applicable.

Period 1

| | |
|------------------------------|--------------------------------|
| Period 1 title | Overall trial (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Not applicable |
| Blinding used | Not blinded |

Blinding implementation details:

Not applicable, open-label trial.

Arms

| | |
|-----------|-------------------|
| Arm title | Enrolled subjects |
|-----------|-------------------|

Arm description:

This was an open-label trial where all enrolled subjects received once weekly i.v. administration of the investigational medicinal product (IMP) velmanase alfa (recombinant lysosomal human alpha-mannosidase). All enrolled subjects were included in the Full Analysis Set and the Safety Analysis Set.

| | |
|--|----------------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Velmanase alfa |
| Investigational medicinal product code | CHFLMZYM |
| Other name | Lamzede |
| Pharmaceutical forms | Powder for solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Velmanase alfa was administered as i.v. infusion once weekly at a dose of 1 mg/kg (weight recorded at first dose and every 4 weeks during the trial). An i.v. catheter could be implanted to ease delivery. The IMP is supplied as a sterile freeze-dried product in single use vials containing 10 mg, each to be reconstituted with 5.0 mL sterile water for injection. Stability of the reconstituted product is 24 hours at 5°C±3°C and 10 hours at a maximum of 25°C. The solution should reach room temperature prior to infusion. Vials were prepared as per the volume required for the dose and swirled with slow rotations for 10-15 seconds after reconstitution. The required volume was withdrawn into one or more large-dose syringes and an infusion set with a mounted filter was filled. The maximum infusion rate was 25 ml/hour. The last empty syringe was replaced with a syringe filled with 20 mL isotonic sodium chloride to infuse the product left in the set.

| Number of subjects in period 1 | Enrolled subjects |
|---|-------------------|
| Started | 8 |
| Completed | 7 |
| Not completed | 1 |
| Went on aftercare programme at local hospital | 1 |

Baseline characteristics

Reporting groups

| | |
|---|--------------------------------|
| Reporting group title | Overall trial (overall period) |
| Reporting group description: | |
| All enrolled subjects were included in the Full Analysis Set and the Safety Analysis Set. | |

| Reporting group values | Overall trial (overall period) | Total | |
|--|--------------------------------|-------|--|
| Number of subjects | 8 | 8 | |
| Age categorical | | | |
| Units: Subjects | | | |
| In utero | 0 | 0 | |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | |
| Newborns (0-27 days) | 0 | 0 | |
| Infants and toddlers (28 days-23 months) | 0 | 0 | |
| Children (2-11 years) | 3 | 3 | |
| Adolescents (12-17 years) | 2 | 2 | |
| Adults (18-64 years) | 3 | 3 | |
| From 65-84 years | 0 | 0 | |
| 85 years and over | 0 | 0 | |
| Age continuous | | | |
| The age is presented as at treatment baseline (i.e. age of subjects at the first ever dose of velmanase alfa including in earlier trials rhLAMAN-02 and rhLAMAN-05). | | | |
| Units: years | | | |
| arithmetic mean | 16.5 | | |
| standard deviation | ± 9.5 | - | |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 3 | 3 | |
| Male | 5 | 5 | |

Subject analysis sets

| | |
|---|---------------------|
| Subject analysis set title | Paediatric subjects |
| Subject analysis set type | Sub-group analysis |
| Subject analysis set description: | |
| Enrolled subjects who were <18 years old at treatment baseline (i.e. when they received the first ever dose of velmanase alfa including in earlier trials rhLAMAN-02 and rhLAMAN-05). | |
| Subject analysis set title | Adult subjects |
| Subject analysis set type | Sub-group analysis |
| Subject analysis set description: | |
| Enrolled subjects who were ≥18 years old at treatment baseline (i.e. when they received the first ever dose of velmanase alfa including in earlier trials rhLAMAN-02 and rhLAMAN-05). | |

| Reporting group values | Paediatric subjects | Adult subjects | |
|------------------------|---------------------|----------------|--|
| Number of subjects | 5 | 3 | |

| | | | |
|--|-------|-------|--|
| Age categorical | | | |
| Units: Subjects | | | |
| In utero | 0 | 0 | |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | |
| Newborns (0-27 days) | 0 | 0 | |
| Infants and toddlers (28 days-23 months) | 0 | 0 | |
| Children (2-11 years) | 3 | 0 | |
| Adolescents (12-17 years) | 2 | 0 | |
| Adults (18-64 years) | 0 | 3 | |
| From 65-84 years | 0 | 0 | |
| 85 years and over | 0 | 0 | |
| Age continuous | | | |
| The age is presented as at treatment baseline (i.e. age of subjects at the first ever dose of velmanase alfa including in earlier trials rhLAMAN-02 and rhLAMAN-05). | | | |
| Units: years | | | |
| arithmetic mean | 10.4 | 26.7 | |
| standard deviation | ± 4.3 | ± 5.8 | |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 2 | 1 | |
| Male | 3 | 2 | |

End points

End points reporting groups

| | |
|--|---------------------|
| Reporting group title | Enrolled subjects |
| Reporting group description: This was an open-label trial where all enrolled subjects received once weekly i.v. administration of the investigational medicinal product (IMP) velmanase alfa (recombinant lysosomal human alpha-mannosidase). All enrolled subjects were included in the Full Analysis Set and the Safety Analysis Set. | |
| Subject analysis set title | Paediatric subjects |
| Subject analysis set type | Sub-group analysis |
| Subject analysis set description: Enrolled subjects who were <18 years old at treatment baseline (i.e. when they received the first ever dose of velmanase alfa including in earlier trials rhLAMAN-02 and rhLAMAN-05). | |
| Subject analysis set title | Adult subjects |
| Subject analysis set type | Sub-group analysis |
| Subject analysis set description: Enrolled subjects who were ≥18 years old at treatment baseline (i.e. when they received the first ever dose of velmanase alfa including in earlier trials rhLAMAN-02 and rhLAMAN-05). | |

Primary: Number of subjects with infusion-related reactions (IRRs)

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|---|--|
| End point title | Number of subjects with infusion-related reactions (IRRs) ^[1] |
| End point description: An adverse drug reaction (ADR) was an AE assessed to be related to study treatment by the Investigator. An IRR was defined as an ADR which occurred during or within 2 hours after the end of the infusion of velmanase alfa and was assessed by the Investigator as being infusion-related. The AEs were classified according to the Medical Dictionary for Regulatory Activities (MedDRA) Version 23.0. The IRRs were summarised by System Organ Class and Preferred Term (PT) overall and by age group. The number of subjects experiencing events is presented by PT. | |
| End point type | Primary |
| End point timeframe: Data for IRRs were collected from enrolment in rhLAMAN-09 until the end of trial. | |
| Notes: [1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point. Justification: As per protocol, data have been presented through listings and when applicable summarised, with no inferential statistics implemented. | |

| End point values | Enrolled subjects | Paediatric subjects | Adult subjects | |
|-----------------------------|-------------------|----------------------|----------------------|--|
| Subject group type | Reporting group | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 8 ^[2] | 5 ^[3] | 3 ^[4] | |
| Units: Subject | | | | |
| Vomiting | 1 | 1 | 0 | |
| Injection site reaction | 1 | 1 | 0 | |
| Injection site swelling | 1 | 1 | 0 | |
| Pyrexia | 1 | 1 | 0 | |
| Dizziness | 1 | 1 | 0 | |
| Tremor | 1 | 1 | 0 | |
| Rash | 1 | 1 | 0 | |

Notes:

[2] - 2 enrolled subjects experienced 7 IRRs.

[3] - 2 paediatric subjects experienced 7 IRRs.

[4] - No adult subjects experienced IRRs.

Statistical analyses

No statistical analyses for this end point

Primary: Detection of ADAs

| | |
|-----------------|----------------------------------|
| End point title | Detection of ADAs ^[5] |
|-----------------|----------------------------------|

End point description:

Detection of ADAs was part of the primary objective and a safety endpoint. Blood samples were collected for ADA assessments pre-infusion during the CEV and every 12 weeks during dose visits. For subjects who had received placebo during rhLAMAN-05, the first ADA assessment was considered as treatment baseline but only if captured not more than 7 days after the first study treatment administration. Subjects were considered to be ADA-positive if they were positive at treatment baseline or had an ADA-positive test at least once during rhLAMAN-09. Subjects were considered to be ADA-negative if they had no ADA-positive tests. At treatment baseline, 6 subjects were ADA-negative and 2 subjects were ADA-positive. The number of subjects who were ADA-positive/negative as defined above, is presented.

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

At treatment baseline (i.e. prior to first ever dose of velmanase alfa including in previous trials) and during rhLAMAN-09.

Notes:

[5] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: As per protocol, data have been presented through listings and when applicable summarised, with no inferential statistics implemented.

| End point values | Enrolled subjects | | | |
|-----------------------------|-------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 8 | | | |
| Units: Subject | | | | |
| ADA-positive | 7 | | | |
| ADA-negative | 1 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute change from treatment baseline to time windows for serum oligosaccharides

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|-----------------|--|
| End point title | Absolute change from treatment baseline to time windows for serum oligosaccharides |
|-----------------|--|

End point description:

Treatment baseline was the last non-missing value before first ever dose of velmanase alfa (including in previous trials if the subject was treated, or in rhLAMAN-09 if the subject received placebo in rhLAMAN-05). Assessments during treatment were assigned to a time point (calculation: date of assessment - date of first ever dose of velmanase alfa)+1). Windowing was performed using the calculated day and a window built around a target day. If >1 time point was reported in the same window, the average of all values was considered in the analysis. Mean (SD) treatment baseline values for enrolled, paediatric and adult subjects were 6.388 (2.232), 7.440 (2.207) and 4.633 (0.551) µmol/L, respectively. For 132-204 and 228-372 weeks, no data were available for any subject. For 60-84, 108-132 and 612-636 weeks, data were available for only 1 enrolled subject (therefore data not shown below). Paired t-test and linear mixed model analyses were performed.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Treatment baseline to time windows from start of treatment (0-12 weeks and 24-weekly intervals)

| End point values | Enrolled subjects | Paediatric subjects | Adult subjects | |
|--------------------------------------|-------------------|----------------------|----------------------|--|
| Subject group type | Reporting group | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 8 | 5 ^[6] | 3 ^[7] | |
| Units: µmol/L | | | | |
| arithmetic mean (standard deviation) | | | | |
| 0-12 weeks | -7.125 (± 1.237) | -7.125 (± 1.237) | 0 (± 0) | |
| 12-36 weeks | -4.683 (± 2.120) | -5.525 (± 2.133) | -3.000 (± 0.566) | |
| 36-60 weeks | -5.511 (± 2.239) | -6.175 (± 2.358) | -3.850 (± 0.354) | |
| 84-108 weeks | -5.306 (± 1.593) | -6.663 (± 0.477) | -3.950 (± 0.177) | |
| 204-228 weeks | -7.638 (± 1.043) | -7.638 (± 1.043) | 0 (± 0) | |
| 372-396 weeks | -3.500 (± 0.889) | 0 (± 0) | -3.000 (± 0.283) | |
| 396-420 weeks | -3.600 (± 0.964) | 0 (± 0) | -3.050 (± 0.212) | |
| 420-444 weeks | -3.933 (± 1.531) | 0 (± 0) | -3.050 (± 0.071) | |
| 444-468 weeks | -3.433 (± 1.623) | -3.517 (± 2.805) | -3.350 (± 0.071) | |
| 468-492 weeks | -3.867 (± 1.601) | 0 (± 0) | -3.050 (± 1.061) | |
| 492-516 weeks | -4.644 (± 2.645) | -5.354 (± 3.106) | -3.225 (± 0.035) | |
| 516-540 weeks | -7.700 (± 0.849) | -7.700 (± 0.849) | 0 (± 0) | |
| 540-564 weeks | -7.950 (± 0.778) | -7.950 (± 0.778) | 0 (± 0) | |
| 564-588 weeks | -7.900 (± 0.990) | -7.900 (± 0.990) | 0 (± 0) | |
| 588-612 weeks | -7.300 (± 0.141) | -7.300 (± 0.141) | 0 (± 0) | |

Notes:

[6] - Data only available for 1 paediatric subject for weeks 372-444 and 468-492, therefore shown as 0.

[7] - No data available for adult subjects for weeks 0-12, 204-228 and 516-636.

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute change from treatment baseline to the CEV for CSF oligosaccharides

| | |
|-----------------|---|
| End point title | Absolute change from treatment baseline to the CEV for CSF oligosaccharides |
|-----------------|---|

End point description:

The mean (SD) treatment baseline values for enrolled, paediatric and adult subjects were 10.900 (3.944), 12.340 (4.474) and 8.500 (0.755) µmol/L, respectively.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

The CEV was performed a mean of 2.5 years from treatment baseline. Absolute change in CSF oligosaccharide concentration from treatment baseline to the CEV was analysed.

| End point values | Enrolled subjects | Paediatric subjects | Adult subjects | |
|--------------------------------------|-------------------|----------------------|----------------------|--|
| Subject group type | Reporting group | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 8 ^[8] | 5 ^[9] | 3 ^[10] | |
| Units: µmol/L | | | | |
| arithmetic mean (standard deviation) | -0.729 (± 2.930) | -0.980 (± 3.549) | -0.100 (± 0.141) | |

Notes:

[8] - 7 enrolled subjects performed the CEV.

[9] - 5 paediatric subjects performed the CEV.

[10] - 2 adult subjects performed the CEV.

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute change from treatment baseline to the CEV for oligosaccharides in 24-hour urine

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|-----------------|--|
| End point title | Absolute change from treatment baseline to the CEV for oligosaccharides in 24-hour urine |
|-----------------|--|

End point description:

Treatment baseline values were available for 2 subjects who were in the paediatric age group (mean (SD) of 904.500 (239.709) µmol/L).

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

The CEV was performed a mean of 2.5 years from treatment baseline. Absolute change in oligosaccharides in 24-hour urine from treatment baseline to the CEV was analysed.

| End point values | Enrolled subjects | Paediatric subjects | Adult subjects | |
|--------------------------------------|---------------------|----------------------|----------------------|--|
| Subject group type | Reporting group | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 8 ^[11] | 5 ^[12] | 3 ^[13] | |
| Units: µmol/L | | | | |
| arithmetic mean (standard deviation) | -532.550 (± 70.216) | -532.550 (± 70.216) | 0 (± 0) | |

Notes:

[11] - Absolute change data only available for 2 subjects (with data at treatment baseline and CEV).

[12] - Absolute change data only available for 2 subjects (who had data at treatment baseline and CEV).

[13] - No absolute change data available as no adult subject had treatment baseline data.

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute change from treatment baseline to time windows for the 6MWT

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|---|--|
| End point title | Absolute change from treatment baseline to time windows for the 6MWT |
| End point description: | |
| Treatment baseline was the last non-missing value before first ever dose of velmanase alfa (including in previous trials if the subject was treated, or in rhLAMAN-09 if the subject received placebo in rhLAMAN-05). Assessments during treatment were assigned to a time point (calculation: date of assessment - date of first ever dose of velmanase alfa)+1). Windowing was performed using the calculated day and a window built around a target day. Six months (183 days) to 365 days were accepted between yearly evaluation visits (rhLAMAN-09); dates >365 days+183 days after a visit belonged to the subsequent visit and dates <183 days from a visit belonged to that visit. Average values were used for analysis if >1 time point was reported in the same window for a subject. Mean (SD) treatment baseline values for enrolled, paediatric and adult subjects were 444.0 (135.0), 411.8 (143.4) and 497.7 (125.7) metres, respectively. Paired t-test and linear mixed model analyses were performed. | |
| End point type | Secondary |
| End point timeframe: | |
| Treatment baseline to 0-6, 6-18, 18-36, 36-60, 60-84, 84-108, 108-132 and 132-156 months (i.e. post-treatment baseline and 1, 2, 4, 6, 8, 10 and 12 years, respectively) from start of treatment. | |

| End point values | Enrolled subjects | Paediatric subjects | Adult subjects | |
|--------------------------------------|-------------------|----------------------|----------------------|--|
| Subject group type | Reporting group | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 8 | 5 | 3 ^[14] | |
| Units: metre | | | | |
| arithmetic mean (standard deviation) | | | | |
| 0-6 months | 42.7 (± 48.6) | 57.0 (± 53.1) | 14.0 (± 29.7) | |
| 1 year | 19.4 (± 84.5) | 31.4 (± 92.4) | -10.5 (± 78.5) | |
| 2 years | 44.9 (± 72.1) | 64.7 (± 70.1) | -4.5 (± 68.6) | |
| 4 years | 41.7 (± 84.4) | 62.2 (± 93.5) | -9.5 (± 20.5) | |
| 6 years | 46.5 (± 74.9) | 79.0 (± 57.5) | -34.8 (± 44.2) | |
| 8 years | 43.0 (± 28.4) | 43.0 (± 28.4) | 0 (± 0) | |
| 10 years | 27.0 (± 105.1) | 103.5 (± 61.5) | -49.5 (± 77.1) | |
| 12 years | 112.5 (± 27.6) | 112.5 (± 27.6) | 0 (± 0) | |

Notes:

[14] - For adult subjects, no data available at 8 and 12 years.

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute change from treatment baseline to time windows for 3MSCT

| | |
|--|---|
| End point title | Absolute change from treatment baseline to time windows for 3MSCT |
| End point description: | |
| Treatment baseline was the last non-missing value before first ever dose of velmanase alfa (including in previous trials if the subject was treated, or in rhLAMAN-09 if the subject received placebo in rhLAMAN-05). Assessments during treatment were assigned to a time point (calculation: date of assessment - date of first ever dose of velmanase alfa)+1). Windowing was performed using the calculated day and a window built around a target day. Six months (183 days) to 365 days were accepted between the yearly evaluation visits (rhLAMAN-09); dates >365 days+183 days after a visit belonged to the next visit and dates <183 days from a visit belonged to that visit. Average values were used for analysis if >1 time point was reported in the same window for a subject. Mean (SD) treatment baseline results for enrolled, paediatric and adult subjects were 51.92 (16.85), 49.73 (19.05) and 55.56 (15.36) steps/minute, respectively. Paired t-test and linear mixed model analyses were performed. | |
| End point type | Secondary |

End point timeframe:

Treatment baseline to 0-6, 6-18, 18-36, 36-60, 60-84, 84-108, 108-132 and 132-156 months (i.e. post-treatment baseline and 1, 2, 4, 6, 8, 10 and 12 years, respectively) from start of treatment.

| End point values | Enrolled subjects | Paediatric subjects | Adult subjects | |
|--------------------------------------|-------------------|----------------------|----------------------|--|
| Subject group type | Reporting group | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 8 | 5 | 3 ^[15] | |
| Units: steps/minute | | | | |
| arithmetic mean (standard deviation) | | | | |
| 0-6 months | 0.83 (± 8.24) | -0.17 (± 10.19) | 2.83 (± 4.01) | |
| 1 year | 3.62 (± 11.25) | 5.40 (± 12.35) | -0.83 (± 9.66) | |
| 2 years | 5.71 (± 9.98) | 8.53 (± 10.64) | -1.33 (± 2.36) | |
| 4 years | 7.41 (± 11.74) | 9.97 (± 13.08) | 1.00 (± 5.19) | |
| 6 years | 3.26 (± 12.27) | 6.83 (± 12.37) | -5.67 (± 8.25) | |
| 8 years | 6.13 (± 15.00) | 6.13 (± 15.00) | 0 (± 0) | |
| 10 years | -3.17 (± 7.56) | 0.83 (± 6.84) | -7.17 (± 7.78) | |
| 12 years | 14.67 (± 0.94) | 14.67 (± 0.94) | 0 (± 0) | |

Notes:

[15] - No data available for adult subjects at 8 and 12 years.

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute change from treatment baseline to time windows for forced vital capacity (FVC) in litres

| | |
|-----------------|---|
| End point title | Absolute change from treatment baseline to time windows for forced vital capacity (FVC) in litres |
|-----------------|---|

End point description:

Treatment baseline was the last non-missing value before first ever dose of velmanase alfa (including in previous trials if the subject was treated, or in rhLAMAN-09 if the subject received placebo in rhLAMAN-05). Assessments during treatment were assigned to a time point (calculation: date of assessment - date of first ever dose of velmanase alfa)+1). Windowing was performed using the calculated day and a window built around a target day. Six months (183 days) to 365 days were accepted between the yearly evaluation visits (rhLAMAN-09); dates >365 days+183 days after a visit belonged to the next visit and dates <183 days from a visit belonged to that visit. Average values were used for analysis if >1 time point was reported in the same window for a subject. Mean (SD) treatment baseline values for enrolled, paediatric and adult subjects were 2.334 (1.041), 1.804 (0.884) and 3.217 (0.600) litres, respectively. Paired t-test and linear mixed model analyses were performed.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Treatment baseline to 0-6, 6-18, 18-36, 36-60, 60-84, 84-108, 108-132 and 132-156 months (i.e. post-treatment baseline and 1, 2, 4, 6, 8, 10 and 12 years, respectively) from start of treatment.

| End point values | Enrolled subjects | Paediatric subjects | Adult subjects | |
|--------------------------------------|-------------------|----------------------|----------------------|--|
| Subject group type | Reporting group | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 8 | 5 | 3 ^[16] | |
| Units: litre(s) | | | | |
| arithmetic mean (standard deviation) | | | | |
| 0-6 months | 0.113 (± 0.430) | -0.008 (± 0.375) | 0.355 (± 0.573) | |
| 1 year | 0.246 (± 0.525) | 0.272 (± 0.636) | 0.180 (± 0.156) | |
| 2 years | 0.411 (± 0.449) | 0.480 (± 0.481) | 0.240 (± 0.453) | |
| 4 years | 0.604 (± 0.733) | 0.644 (± 0.813) | 0.505 (± 0.742) | |
| 6 years | 0.842 (± 0.941) | 0.955 (± 0.966) | 0.560 (± 1.167) | |
| 8 years | 1.389 (± 1.038) | 1.389 (± 1.038) | 0 (± 0) | |
| 10 years | 0.970 (± 1.098) | 1.575 (± 1.266) | 0.365 (± 0.742) | |
| 12 years | 1.650 (± 0.622) | 1.650 (± 0.622) | 0 (± 0) | |

Notes:

[16] - No data available for adult subjects at 8 and 12 years.

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute change from treatment baseline to time windows for FVC percent predicted

| | |
|-----------------|---|
| End point title | Absolute change from treatment baseline to time windows for FVC percent predicted |
|-----------------|---|

End point description:

Treatment baseline was the last non-missing value before first ever dose of velmanase alfa (including in previous trials if the subject was treated, or in rhLAMAN-09 if the subject received placebo in rhLAMAN-05). Assessments during treatment were assigned to a time point (calculation: date of assessment - date of first ever dose of velmanase alfa)+1). Windowing was performed using the calculated day and a window built around a target day. Six months (183 days) to 365 days were accepted between the yearly evaluation visits (rhLAMAN-09); dates >365 days+183 days after a visit belonged to the next visit and dates <183 days from a visit belonged to that visit. Average values were used for analysis if >1 time point was reported in the same window for a subject. Mean (SD) treatment baseline values for enrolled, paediatric and adult subjects were 83.5 (22.8)%, 80.1 (25.3)% and 89.0 (21.7)%, respectively. Paired t-test and linear mixed model analyses were performed.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Treatment baseline to 0-6, 6-18, 18-36, 36-60, 60-84, 84-108, 108-132 and 132-156 months (i.e. post-treatment baseline and 1, 2, 4, 6, 8, 10 and 12 years, respectively) from start of treatment.

| End point values | Enrolled subjects | Paediatric subjects | Adult subjects | |
|--------------------------------------|-------------------|----------------------|----------------------|--|
| Subject group type | Reporting group | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 8 | 5 | 3 ^[17] | |
| Units: percentage | | | | |
| arithmetic mean (standard deviation) | | | | |
| 0-6 months | -5.6 (± 25.3) | -13.4 (± 26.6) | 10.0 (± 18.4) | |
| 1 year | -0.2 (± 25.5) | -2.6 (± 30.5) | 6.0 (± 8.5) | |
| 2 years | 3.1 (± 22.9) | 1.3 (± 26.6) | 7.5 (± 16.3) | |
| 4 years | 3.0 (± 32.9) | -1.6 (± 37.5) | 14.5 (± 22.6) | |
| 6 years | 5.3 (± 36.1) | 1.2 (± 40.0) | 15.8 (± 33.6) | |
| 8 years | 15.0 (± 33.5) | 15.0 (± 33.5) | 0 (± 0) | |
| 10 years | -10.5 (± 30.4) | -17.5 (± 41.7) | -3.5 (± 29.0) | |
| 12 years | 9.2 (± 28.0) | 9.2 (± 28.0) | 0 (± 0) | |

Notes:

[17] - No data available for adult subjects at 8 and 12 years.

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute change from treatment baseline to time windows for forced expiratory volume in the first second (FEV1) (litres)

| | |
|-----------------|--|
| End point title | Absolute change from treatment baseline to time windows for forced expiratory volume in the first second (FEV1) (litres) |
|-----------------|--|

End point description:

Treatment baseline was the last non-missing value before first ever dose of velmanase alfa (including in previous trials if the subject was treated, or in rhLAMAN-09 if the subject received placebo in rhLAMAN-05). Assessments during treatment were assigned to a time point (calculation: date of assessment - date of first ever dose of velmanase alfa)+1). Windowing was performed using the calculated day and a window built around a target day. Six months (183 days) to 365 days were accepted between the yearly evaluation visits (rhLAMAN-09); dates >365 days+183 days after a visit belonged to the next visit and dates <183 days from a visit belonged to that visit. Average values were used for analysis if >1 time point was reported in the same window for a subject. Mean (SD) treatment baseline values for enrolled, paediatric and adult subjects were 2.076 (0.972), 1.608 (0.828) and 2.857 (0.690) litres, respectively. Paired t-test and linear mixed model analyses were performed.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Treatment baseline to 0-6, 6-18, 18-36, 36-60, 60-84, 84-108, 108-132 and 132-156 months (i.e. post-treatment baseline and 1, 2, 4, 6, 8, 10 and 12 years, respectively) from start of treatment.

| End point values | Enrolled subjects | Paediatric subjects | Adult subjects | |
|--------------------------------------|-------------------|----------------------|----------------------|--|
| Subject group type | Reporting group | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 8 | 5 | 3 ^[18] | |
| Units: litre(s) | | | | |
| arithmetic mean (standard deviation) | | | | |
| 0-6 months | 0.302 (± 0.530) | 0.113 (± 0.405) | 0.585 (± 0.728) | |
| 1 year | 0.241 (± 0.468) | 0.235 (± 0.474) | 0.255 (± 0.643) | |
| 2 years | 0.289 (± 0.447) | 0.191 (± 0.404) | 0.535 (± 0.615) | |

| | | | | |
|----------|-----------------|-----------------|-----------------|--|
| 4 years | 0.662 (± 1.058) | 0.651 (± 1.222) | 0.690 (± 0.856) | |
| 6 years | 0.854 (± 0.902) | 0.871 (± 0.869) | 0.813 (± 1.361) | |
| 8 years | 1.248 (± 0.799) | 1.248 (± 0.799) | 0 (± 0) | |
| 10 years | 1.253 (± 0.939) | 1.870 (± 0.354) | 0.635 (± 0.997) | |
| 12 years | 0.885 (± 0.587) | 0.885 (± 0.587) | 0 (± 0) | |

Notes:

[18] - No data available for adult subjects at 8 and 12 years.

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute change from treatment baseline to time windows for FEV1 percent predicted

| | |
|-----------------|--|
| End point title | Absolute change from treatment baseline to time windows for FEV1 percent predicted |
|-----------------|--|

End point description:

Treatment baseline was the last non-missing value before first ever dose of velmanase alfa (including in previous trials if the subject was treated, or in rhLAMAN-09 if the subject received placebo in rhLAMAN-05). Assessments during treatment were assigned to a time point (calculation: date of assessment - date of first ever dose of velmanase alfa)+1). Windowing was performed using the calculated day and a window built around a target day. Six months (183 days) to 365 days were accepted between the yearly evaluation visits (rhLAMAN-09); dates >365 days+183 days after a visit belonged to the next visit and dates <183 days from a visit belonged to that visit. Average values were used for analysis if >1 time point was reported in the same window for a subject. Mean (SD) treatment baseline values for enrolled, paediatric and adult subjects were 78.2 (16.7)%, 74.3 (11.8)% and 84.7 (24.4)%, respectively. Paired t-test and linear mixed model analyses were performed.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Treatment baseline to 0-6, 6-18, 18-36, 36-60, 60-84, 84-108, 108-132 and 132-156 months (i.e. post-treatment baseline and 1, 2, 4, 6, 8, 10 and 12 years, respectively) from start of treatment.

| End point values | Enrolled subjects | Paediatric subjects | Adult subjects | |
|--------------------------------------|-------------------|----------------------|----------------------|--|
| Subject group type | Reporting group | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 8 | 5 | 3 ^[19] | |
| Units: percentage | | | | |
| arithmetic mean (standard deviation) | | | | |
| 0-6 months | 3.1 (± 22.8) | -5.9 (± 21.7) | 16.5 (± 23.3) | |
| 1 year | 1.4 (± 22.0) | -1.0 (± 24.1) | 7.5 (± 21.9) | |
| 2 years | 0.3 (± 20.0) | -6.0 (± 17.8) | 16.0 (± 21.2) | |
| 4 years | 1.0 (± 25.6) | -6.5 (± 23.4) | 19.8 (± 27.2) | |
| 6 years | 8.8 (± 30.6) | 3.1 (± 29.0) | 23.0 (± 41.0) | |
| 8 years | 14.0 (± 28.5) | 14.0 (± 28.5) | 0 (± 0) | |
| 10 years | 13.3 (± 22.1) | 13.5 (± 2.1) | 13.0 (± 38.2) | |
| 12 years | -3.3 (± 35.8) | -3.3 (± 35.8) | 0 (± 0) | |

Notes:

[19] - No data available for adult subjects at 8 and 12 years.

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute change from treatment baseline to time windows for peak expiratory flow (PEF)

| | |
|-----------------|--|
| End point title | Absolute change from treatment baseline to time windows for peak expiratory flow (PEF) |
|-----------------|--|

End point description:

Treatment baseline was the last non-missing value before first ever dose of velmanase alfa (including in previous trials if the subject was treated, or in rhLAMAN-09 if the subject received placebo in rhLAMAN-05). Assessments during treatment were assigned to a time point (calculation: date of assessment - date of first ever dose of velmanase alfa)+1). Windowing was performed using the calculated day and a window built around a target day. Six months (183 days) to 365 days were accepted between the yearly evaluation visits (rhLAMAN-09); dates >365 days+183 days after a visit belonged to the next visit and dates <183 days from a visit belonged to that visit. Average values were used for analysis if >1 time point was reported in the same window for a subject. Mean (SD) treatment baseline values for enrolled, paediatric and adult subjects were 4.166 (2.540), 3.032 (1.849) and 6.057 (2.676) litres per second, respectively. Paired t-test and linear mixed model analyses were performed.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Treatment baseline to 0-6, 6-18, 18-36, 36-60, 60-84, 84-108, 108-132 and 132-156 months (i.e. post-treatment baseline and 1, 2, 4, 6, 8, 10 and 12 years, respectively) from start of treatment.

| End point values | Enrolled subjects | Paediatric subjects | Adult subjects | |
|--------------------------------------|-------------------|----------------------|----------------------|--|
| Subject group type | Reporting group | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 8 | 5 | 3 ^[20] | |
| Units: litres per second | | | | |
| arithmetic mean (standard deviation) | | | | |
| 0-6 months | 1.125 (± 1.492) | 0.803 (± 0.702) | 1.770 (± 2.899) | |
| 1 year | 0.679 (± 1.481) | 0.322 (± 1.212) | 1.570 (± 2.249) | |
| 2 years | 1.269 (± 2.180) | 0.394 (± 1.509) | 3.455 (± 2.454) | |
| 4 years | 1.289 (± 2.592) | 0.516 (± 1.781) | 3.220 (± 4.144) | |
| 6 years | 2.376 (± 2.795) | 2.307 (± 1.967) | 2.548 (± 5.597) | |
| 8 years | 2.919 (± 2.389) | 2.919 (± 2.389) | 0 (± 0) | |
| 10 years | 3.593 (± 2.302) | 4.800 (± 2.079) | 2.385 (± 2.397) | |
| 12 years | 1.360 (± 0.863) | 1.360 (± 0.863) | 0 (± 0) | |

Notes:

[20] - No data available for adult subjects at 8 and 12 years.

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute change from treatment baseline to time windows for CHAQ Disability Index

| | |
|-----------------|---|
| End point title | Absolute change from treatment baseline to time windows for CHAQ Disability Index |
|-----------------|---|

End point description:

Treatment baseline was the last non-missing value before first ever dose of velmanase alfa (also in previous trials if the subject was treated, or in rhLAMAN-09 if the subject received placebo in rhLAMAN-05). Assessments during treatment were assigned to a time point (calculation: date of assessment - date of first ever dose of velmanase alfa)+1). Windowing was performed using the calculated day and a window built around a target day. Six months (183 days) to 365 days were accepted between the yearly evaluation visits (rhLAMAN-09); dates >365 days+183 days after a visit belonged to the next visit and dates <183 days from a visit belonged to that visit. Average values were used for analysis if >1 time point was reported in the same window for a subject. Mean (SD) treatment baseline scores for enrolled, paediatric and adult subjects were 1.422 (0.853), 1.350 (1.112) and 1.542 (0.191), respectively. The CHAQ Disability Index is scored 0-3 with higher scores indicating greater disability.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Treatment baseline to 0-6, 6-18, 18-36, 36-60, 60-84, 84-108, 108-132 and 132-156 months (i.e. post-treatment baseline and 1, 2, 4, 6, 8, 10 and 12 years, respectively) from start of treatment.

| End point values | Enrolled subjects | Paediatric subjects | Adult subjects | |
|--------------------------------------|-------------------|----------------------|----------------------|--|
| Subject group type | Reporting group | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 8 | 5 | 3 ^[21] | |
| Units: score | | | | |
| arithmetic mean (standard deviation) | | | | |
| 0-6 months | 0.104 (± 0.635) | 0.000 (± 0.791) | 0.313 (± 0.088) | |
| 1 year | -0.116 (± 0.379) | -0.188 (± 0.380) | 0.063 (± 0.442) | |
| 2 years | -0.136 (± 0.513) | -0.341 (± 0.425) | 0.375 (± 0.354) | |
| 4 years | -0.125 (± 0.784) | -0.325 (± 0.854) | 0.375 (± 0.265) | |
| 6 years | 0.179 (± 0.890) | 0.038 (± 1.049) | 0.531 (± 0.044) | |
| 8 years | -0.391 (± 0.531) | -0.391 (± 0.531) | 0 (± 0) | |
| 10 years | 0.240 (± 0.862) | -0.146 (± 1.267) | 0.625 (± 0.177) | |
| 12 years | 0.375 (± 0.177) | 0.375 (± 0.177) | 0 (± 0) | |

Notes:

[21] - No data available for adult subjects at 8 and 12 years.

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute change from treatment baseline to time windows for CHAQ Visual Analogue Scale (VAS) Pain

| | |
|-----------------|---|
| End point title | Absolute change from treatment baseline to time windows for CHAQ Visual Analogue Scale (VAS) Pain |
|-----------------|---|

End point description:

Treatment baseline was the last non-missing value before first ever dose of velmanase alfa (including in previous trials if the subject was treated, or in rhLAMAN-09 if the subject received placebo in rhLAMAN-05). Assessments during treatment were assigned to a time point (calculation: date of assessment - date of first ever dose of velmanase alfa)+1). Windowing was performed using the calculated day and a window built around a target day. Six months (183 days) to 365 days were accepted between the yearly evaluation visits (rhLAMAN-09); dates >365 days+183 days after a visit belonged to the next visit and dates <183 days from a visit belonged to that visit. Average values were used for analysis if >1 time point was reported in the same window for a subject. Mean (SD) treatment baseline scores for enrolled, paediatric and adult subjects were 0.675 (0.496), 0.522 (0.450) and 0.930 (0.546), respectively. The CHAQ VAS Pain is scored 0 (no pain) to 3 (very severe pain).

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Treatment baseline to 0-6, 6-18, 18-36, 36-60, 60-84, 84-108, 108-132 and 132-156 months (i.e. post-treatment baseline and 1, 2, 4, 6, 8, 10 and 12 years, respectively) from start of treatment.

| End point values | Enrolled subjects | Paediatric subjects | Adult subjects | |
|--------------------------------------|-------------------|----------------------|----------------------|--|
| Subject group type | Reporting group | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 8 | 5 | 3 ^[22] | |
| Units: score | | | | |
| arithmetic mean (standard deviation) | | | | |
| 0-6 months | 0.225 (± 0.286) | 0.225 (± 0.367) | 0.225 (± 0.064) | |
| 1 year | -0.251 (± 0.567) | -0.159 (± 0.659) | -0.480 (± 0.212) | |
| 2 years | -0.026 (± 0.572) | -0.102 (± 0.681) | 0.165 (± 0.106) | |
| 4 years | 0.178 (± 0.664) | 0.012 (± 0.734) | 0.593 (± 0.074) | |
| 6 years | 0.467 (± 0.555) | 0.267 (± 0.512) | 0.968 (± 0.308) | |
| 8 years | 0.173 (± 0.573) | 0.173 (± 0.573) | 0 (± 0) | |
| 10 years | 0.660 (± 0.748) | 0.750 (± 1.061) | 0.570 (± 0.721) | |
| 12 years | 0.105 (± 0.827) | 0.105 (± 0.827) | 0 (± 0) | |

Notes:

[22] - No data available for adult subjects at 8 and 12 years.

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute change from treatment baseline to time windows for CHAQ VAS General

| | |
|-----------------|--|
| End point title | Absolute change from treatment baseline to time windows for CHAQ VAS General |
|-----------------|--|

End point description:

Treatment baseline was the last non-missing value before first ever dose of velmanase alfa (also in previous trials if the subject was treated, or in rhLAMAN-09 if the subject received placebo in rhLAMAN-05). Assessments during treatment were assigned to a time point (calculation: date of assessment - date of first ever dose of velmanase alfa)+1). Windowing was performed using the calculated day and a window built around a target day. Six months (183 days) to 365 days were accepted between the yearly evaluation visits (rhLAMAN-09); dates >365 days+183 days after a visit belonged to the next visit and dates <183 days from a visit belonged to that visit. Average values were used for analysis if >1 time point was reported in the same window for a subject. Mean (SD) treatment baseline scores for enrolled, paediatric and adult subjects were 0.668 (0.546), 0.480 (0.603) and 0.980 (0.284), respectively. The CHAQ VAS General is scored 0-3 with higher scores indicating poorer quality of life.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Treatment baseline to 0-6, 6-18, 18-36, 36-60, 60-84, 84-108, 108-132 and 132-156 months (i.e. post-treatment baseline and 1, 2, 4, 6, 8, 10 and 12 years, respectively) from start of treatment.

| End point values | Enrolled subjects | Paediatric subjects | Adult subjects | |
|--------------------------------------|-------------------|----------------------|----------------------|--|
| Subject group type | Reporting group | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 8 | 5 | 3 ^[23] | |
| Units: score | | | | |
| arithmetic mean (standard deviation) | | | | |
| 0-6 months | 0.290 (± 0.877) | 0.488 (± 1.046) | -0.105 (± 0.318) | |
| 1 year | -0.041 (± 0.827) | -0.093 (± 1.005) | 0.090 (± 0.127) | |
| 2 years | -0.129 (± 0.550) | -0.120 (± 0.632) | -0.150 (± 0.467) | |
| 4 years | 0.351 (± 0.699) | 0.279 (± 0.839) | 0.533 (± 0.159) | |
| 6 years | 0.403 (± 0.670) | 0.339 (± 0.809) | 0.563 (± 0.011) | |
| 8 years | 0.308 (± 0.385) | 0.308 (± 0.385) | 0 (± 0) | |
| 10 years | 0.585 (± 0.658) | 0.750 (± 1.061) | 0.420 (± 0.255) | |
| 12 years | 0.060 (± 0.212) | 0.060 (± 0.212) | 0 (± 0) | |

Notes:

[23] - No data available for adult subjects at 8 and 12 years.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Treatment-emergent adverse events (TEAEs) were collected from the time of informed consent in rhLAMAN-09, for the duration of the trial.

Adverse event reporting additional description:

All TEAEs were collected from spontaneous, unsolicited reports of subjects, by observation and by routine open questioning.

| | |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

Dictionary used

| | |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|------|
| Dictionary version | 23.0 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|-------------------|
| Reporting group title | Enrolled subjects |
|-----------------------|-------------------|

Reporting group description:

This was an open-label trial where all enrolled subjects received once weekly i.v. administration of the IMP velmanase alfa (recombinant human lysosomal alpha-mannosidase). All enrolled subjects were included in the Full Analysis Set and the Safety Analysis Set.

| | |
|-----------------------|---------------------|
| Reporting group title | Paediatric subjects |
|-----------------------|---------------------|

Reporting group description:

Subjects aged <18 years at the time of first ever dose of velmanase alfa.

| | |
|-----------------------|----------------|
| Reporting group title | Adult subjects |
|-----------------------|----------------|

Reporting group description:

Subjects aged ≥18 years at the time of first ever dose of velmanase alfa.

| Serious adverse events | Enrolled subjects | Paediatric subjects | Adult subjects |
|---|-------------------|---------------------|----------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 2 / 8 (25.00%) | 2 / 5 (40.00%) | 0 / 3 (0.00%) |
| number of deaths (all causes) | 0 | 0 | 0 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Systemic lupus erythematosus | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 1 / 5 (20.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 3 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| Pneumonia | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 1 / 5 (20.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ear infection | | | |

| | | | |
|---|----------------|----------------|---------------|
| subjects affected / exposed | 1 / 8 (12.50%) | 1 / 5 (20.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Subcutaneous abscess | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 1 / 5 (20.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

Frequency threshold for reporting non-serious adverse events: 5 %

| Non-serious adverse events | Enrolled subjects | Paediatric subjects | Adult subjects |
|---|-------------------|---------------------|----------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 7 / 8 (87.50%) | 5 / 5 (100.00%) | 2 / 3 (66.67%) |
| Vascular disorders | | | |
| Extravasation blood | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 1 / 5 (20.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Hypertension | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 5 (0.00%) | 1 / 3 (33.33%) |
| occurrences (all) | 1 | 0 | 1 |
| Surgical and medical procedures | | | |
| Central venous catheterisation | | | |
| subjects affected / exposed | 2 / 8 (25.00%) | 2 / 5 (40.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 2 | 2 | 0 |
| Cochlea implant | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 1 / 5 (20.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Ear operation | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 1 / 5 (20.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Endodontic procedure | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 1 / 5 (20.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Eye operation | | | |

| | | | |
|--|----------------|----------------|----------------|
| subjects affected / exposed | 1 / 8 (12.50%) | 1 / 5 (20.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Hearing aid therapy | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 1 / 5 (20.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Tooth extraction | | | |
| subjects affected / exposed | 2 / 8 (25.00%) | 2 / 5 (40.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 3 | 3 | 0 |
| General disorders and administration site conditions | | | |
| Axillary pain | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 1 / 5 (20.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Chest pain | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 1 / 5 (20.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Fatigue | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 1 / 5 (20.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Impaired healing | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 5 (0.00%) | 1 / 3 (33.33%) |
| occurrences (all) | 1 | 0 | 1 |
| Inflammation | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 5 (0.00%) | 1 / 3 (33.33%) |
| occurrences (all) | 1 | 0 | 1 |
| Infusion site swelling | | | |
| subjects affected / exposed | 3 / 8 (37.50%) | 2 / 5 (40.00%) | 1 / 3 (33.33%) |
| occurrences (all) | 3 | 2 | 1 |
| Injection site reaction | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 1 / 5 (20.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 3 | 3 | 0 |
| Injection site swelling | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 1 / 5 (20.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 3 | 3 | 0 |
| Peripheral swelling | | | |

| | | | |
|---|----------------------|-----------------------|---------------------|
| subjects affected / exposed occurrences (all) | 1 / 8 (12.50%) 1 | 0 / 5 (0.00%) 0 | 1 / 3 (33.33%) 1 |
| Pyrexia subjects affected / exposed occurrences (all) | 6 / 8 (75.00%) 28 | 5 / 5 (100.00%) 24 | 1 / 3 (33.33%) 4 |
| Swelling face subjects affected / exposed occurrences (all) | 1 / 8 (12.50%) 1 | 1 / 5 (20.00%) 1 | 0 / 3 (0.00%) 0 |
| Immune system disorders Hypersensitivity subjects affected / exposed occurrences (all) | 1 / 8 (12.50%) 2 | 1 / 5 (20.00%) 2 | 0 / 3 (0.00%) 0 |
| Multiple allergies subjects affected / exposed occurrences (all) | 1 / 8 (12.50%) 1 | 1 / 5 (20.00%) 1 | 0 / 3 (0.00%) 0 |
| Seasonal allergy subjects affected / exposed occurrences (all) | 1 / 8 (12.50%) 1 | 1 / 5 (20.00%) 1 | 0 / 3 (0.00%) 0 |
| Reproductive system and breast disorders Dysmenorrhoea subjects affected / exposed occurrences (all) | 1 / 8 (12.50%) 1 | 1 / 5 (20.00%) 1 | 0 / 3 (0.00%) 0 |
| Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all) | 4 / 8 (50.00%) 8 | 4 / 5 (80.00%) 8 | 0 / 3 (0.00%) 0 |
| Obstructive airways disorder subjects affected / exposed occurrences (all) | 1 / 8 (12.50%) 1 | 1 / 5 (20.00%) 1 | 0 / 3 (0.00%) 0 |
| Oropharyngeal pain subjects affected / exposed occurrences (all) | 3 / 8 (37.50%) 4 | 1 / 5 (20.00%) 2 | 2 / 3 (66.67%) 2 |
| Rhinorrhoea subjects affected / exposed occurrences (all) | 2 / 8 (25.00%) 2 | 2 / 5 (40.00%) 2 | 0 / 3 (0.00%) 0 |
| Psychiatric disorders | | | |

| | | | |
|--|---------------------|---------------------|---------------------|
| Aggression subjects affected / exposed occurrences (all) | 1 / 8 (12.50%) 1 | 1 / 5 (20.00%) 1 | 0 / 3 (0.00%) 0 |
| Psychotic disorder subjects affected / exposed occurrences (all) | 1 / 8 (12.50%) 1 | 0 / 5 (0.00%) 0 | 1 / 3 (33.33%) 1 |
| Investigations | | | |
| Nitrite urine present subjects affected / exposed occurrences (all) | 1 / 8 (12.50%) 1 | 1 / 5 (20.00%) 1 | 0 / 3 (0.00%) 0 |
| Weight increased subjects affected / exposed occurrences (all) | 1 / 8 (12.50%) 1 | 1 / 5 (20.00%) 1 | 0 / 3 (0.00%) 0 |
| White blood cells urine positive subjects affected / exposed occurrences (all) | 1 / 8 (12.50%) 1 | 1 / 5 (20.00%) 1 | 0 / 3 (0.00%) 0 |
| Injury, poisoning and procedural complications | | | |
| Arthropod bite subjects affected / exposed occurrences (all) | 1 / 8 (12.50%) 1 | 1 / 5 (20.00%) 1 | 0 / 3 (0.00%) 0 |
| Buttock injury subjects affected / exposed occurrences (all) | 1 / 8 (12.50%) 1 | 1 / 5 (20.00%) 1 | 0 / 3 (0.00%) 0 |
| Contusion subjects affected / exposed occurrences (all) | 2 / 8 (25.00%) 4 | 2 / 5 (40.00%) 4 | 0 / 3 (0.00%) 0 |
| Face injury subjects affected / exposed occurrences (all) | 3 / 8 (37.50%) 3 | 1 / 5 (20.00%) 1 | 2 / 3 (66.67%) 2 |
| Foot fracture subjects affected / exposed occurrences (all) | 1 / 8 (12.50%) 1 | 1 / 5 (20.00%) 1 | 0 / 3 (0.00%) 0 |
| Hand fracture subjects affected / exposed occurrences (all) | 1 / 8 (12.50%) 1 | 1 / 5 (20.00%) 1 | 0 / 3 (0.00%) 0 |
| Head injury | | | |

| | | | |
|-----------------------------|----------------|----------------|----------------|
| subjects affected / exposed | 2 / 8 (25.00%) | 1 / 5 (20.00%) | 1 / 3 (33.33%) |
| occurrences (all) | 2 | 1 | 1 |
| Ligament sprain | | | |
| subjects affected / exposed | 3 / 8 (37.50%) | 2 / 5 (40.00%) | 1 / 3 (33.33%) |
| occurrences (all) | 4 | 2 | 2 |
| Limb injury | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 1 / 5 (20.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Post procedural swelling | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 1 / 5 (20.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Procedural pain | | | |
| subjects affected / exposed | 2 / 8 (25.00%) | 2 / 5 (40.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 2 | 2 | 0 |
| Scratch | | | |
| subjects affected / exposed | 2 / 8 (25.00%) | 2 / 5 (40.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 3 | 3 | 0 |
| Skin abrasion | | | |
| subjects affected / exposed | 3 / 8 (37.50%) | 2 / 5 (40.00%) | 1 / 3 (33.33%) |
| occurrences (all) | 6 | 4 | 2 |
| Skin wound | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 1 / 5 (20.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Tooth fracture | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 1 / 5 (20.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Wound | | | |
| subjects affected / exposed | 3 / 8 (37.50%) | 2 / 5 (40.00%) | 1 / 3 (33.33%) |
| occurrences (all) | 6 | 5 | 1 |
| Wound complication | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 1 / 5 (20.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Nervous system disorders | | | |
| Dizziness | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 1 / 5 (20.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 4 | 4 | 0 |

| | | | |
|---|----------------------|----------------------|---------------------|
| Dysarthria subjects affected / exposed occurrences (all) | 1 / 8 (12.50%) 1 | 1 / 5 (20.00%) 1 | 0 / 3 (0.00%) 0 |
| Headache subjects affected / exposed occurrences (all) | 1 / 8 (12.50%) 19 | 1 / 5 (20.00%) 19 | 0 / 3 (0.00%) 0 |
| Syncope subjects affected / exposed occurrences (all) | 1 / 8 (12.50%) 1 | 1 / 5 (20.00%) 1 | 0 / 3 (0.00%) 0 |
| Tremor subjects affected / exposed occurrences (all) | 1 / 8 (12.50%) 1 | 1 / 5 (20.00%) 1 | 0 / 3 (0.00%) 0 |
| Blood and lymphatic system disorders Lymphadenopathy subjects affected / exposed occurrences (all) | 1 / 8 (12.50%) 1 | 1 / 5 (20.00%) 1 | 0 / 3 (0.00%) 0 |
| Ear and labyrinth disorders Ear disorder subjects affected / exposed occurrences (all) | 1 / 8 (12.50%) 1 | 0 / 5 (0.00%) 0 | 1 / 3 (33.33%) 1 |
| Ear pain subjects affected / exposed occurrences (all) | 2 / 8 (25.00%) 6 | 2 / 5 (40.00%) 6 | 0 / 3 (0.00%) 0 |
| Otorrhoea subjects affected / exposed occurrences (all) | 1 / 8 (12.50%) 3 | 0 / 5 (0.00%) 0 | 1 / 3 (33.33%) 3 |
| Eye disorders Conjunctivitis allergic subjects affected / exposed occurrences (all) | 1 / 8 (12.50%) 2 | 1 / 5 (20.00%) 2 | 0 / 3 (0.00%) 0 |
| Eye allergy subjects affected / exposed occurrences (all) | 1 / 8 (12.50%) 1 | 1 / 5 (20.00%) 1 | 0 / 3 (0.00%) 0 |
| Eye pruritus subjects affected / exposed occurrences (all) | 1 / 8 (12.50%) 3 | 1 / 5 (20.00%) 3 | 0 / 3 (0.00%) 0 |
| Gastrointestinal disorders | | | |

| | | | |
|----------------------------------|----------------|----------------|----------------|
| Abdominal pain upper | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 1 / 5 (20.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Diarrhoea | | | |
| subjects affected / exposed | 3 / 8 (37.50%) | 3 / 5 (60.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 5 | 5 | 0 |
| Duodenitis | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 1 / 5 (20.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Gastritis | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 5 (0.00%) | 1 / 3 (33.33%) |
| occurrences (all) | 1 | 0 | 1 |
| Gastrooesophageal reflux disease | | | |
| subjects affected / exposed | 2 / 8 (25.00%) | 1 / 5 (20.00%) | 1 / 3 (33.33%) |
| occurrences (all) | 8 | 7 | 1 |
| Glossitis | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 1 / 5 (20.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Inguinal hernia | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 1 / 5 (20.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Nausea | | | |
| subjects affected / exposed | 2 / 8 (25.00%) | 1 / 5 (20.00%) | 1 / 3 (33.33%) |
| occurrences (all) | 3 | 2 | 1 |
| Oesophagitis | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 1 / 5 (20.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Salivary gland enlargement | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 1 / 5 (20.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Stomatitis | | | |
| subjects affected / exposed | 2 / 8 (25.00%) | 2 / 5 (40.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 2 | 2 | 0 |
| Tooth loss | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 1 / 5 (20.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |

| | | | |
|---|----------------------|----------------------|---------------------|
| Toothache subjects affected / exposed occurrences (all) | 1 / 8 (12.50%) 1 | 0 / 5 (0.00%) 0 | 1 / 3 (33.33%) 1 |
| Vomiting subjects affected / exposed occurrences (all) | 7 / 8 (87.50%) 10 | 5 / 5 (100.00%) 8 | 2 / 3 (66.67%) 2 |
| Skin and subcutaneous tissue disorders | | | |
| Acne subjects affected / exposed occurrences (all) | 1 / 8 (12.50%) 3 | 1 / 5 (20.00%) 3 | 0 / 3 (0.00%) 0 |
| Eczema subjects affected / exposed occurrences (all) | 1 / 8 (12.50%) 1 | 1 / 5 (20.00%) 1 | 0 / 3 (0.00%) 0 |
| Erythema subjects affected / exposed occurrences (all) | 1 / 8 (12.50%) 1 | 0 / 5 (0.00%) 0 | 1 / 3 (33.33%) 1 |
| Nail bed inflammation subjects affected / exposed occurrences (all) | 1 / 8 (12.50%) 2 | 1 / 5 (20.00%) 2 | 0 / 3 (0.00%) 0 |
| Rash subjects affected / exposed occurrences (all) | 1 / 8 (12.50%) 1 | 1 / 5 (20.00%) 1 | 0 / 3 (0.00%) 0 |
| Rash erythematous subjects affected / exposed occurrences (all) | 1 / 8 (12.50%) 1 | 0 / 5 (0.00%) 0 | 1 / 3 (33.33%) 1 |
| Renal and urinary disorders | | | |
| Dysuria subjects affected / exposed occurrences (all) | 2 / 8 (25.00%) 2 | 1 / 5 (20.00%) 1 | 1 / 3 (33.33%) 1 |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia subjects affected / exposed occurrences (all) | 4 / 8 (50.00%) 5 | 3 / 5 (60.00%) 4 | 1 / 3 (33.33%) 1 |
| Back pain subjects affected / exposed occurrences (all) | 2 / 8 (25.00%) 4 | 0 / 5 (0.00%) 0 | 2 / 3 (66.67%) 4 |

| | | | |
|--|----------------------|----------------------|---------------------|
| Intervertebral disc disorder subjects affected / exposed occurrences (all) | 1 / 8 (12.50%) 1 | 0 / 5 (0.00%) 0 | 1 / 3 (33.33%) 1 |
| Joint swelling subjects affected / exposed occurrences (all) | 1 / 8 (12.50%) 1 | 1 / 5 (20.00%) 1 | 0 / 3 (0.00%) 0 |
| Pain in extremity subjects affected / exposed occurrences (all) | 2 / 8 (25.00%) 2 | 2 / 5 (40.00%) 2 | 0 / 3 (0.00%) 0 |
| Systemic lupus erythematosus subjects affected / exposed occurrences (all) | 1 / 8 (12.50%) 1 | 1 / 5 (20.00%) 1 | 0 / 3 (0.00%) 0 |
| Infections and infestations | | | |
| Abscess limb subjects affected / exposed occurrences (all) | 1 / 8 (12.50%) 1 | 1 / 5 (20.00%) 1 | 0 / 3 (0.00%) 0 |
| Abscess oral subjects affected / exposed occurrences (all) | 1 / 8 (12.50%) 1 | 1 / 5 (20.00%) 1 | 0 / 3 (0.00%) 0 |
| Bronchitis subjects affected / exposed occurrences (all) | 1 / 8 (12.50%) 1 | 1 / 5 (20.00%) 1 | 0 / 3 (0.00%) 0 |
| COVID-19 subjects affected / exposed occurrences (all) | 1 / 8 (12.50%) 2 | 1 / 5 (20.00%) 2 | 0 / 3 (0.00%) 0 |
| Conjunctivitis subjects affected / exposed occurrences (all) | 1 / 8 (12.50%) 1 | 1 / 5 (20.00%) 1 | 0 / 3 (0.00%) 0 |
| Device related infection subjects affected / exposed occurrences (all) | 1 / 8 (12.50%) 1 | 1 / 5 (20.00%) 1 | 0 / 3 (0.00%) 0 |
| Ear infection subjects affected / exposed occurrences (all) | 5 / 8 (62.50%) 18 | 4 / 5 (80.00%) 11 | 1 / 3 (33.33%) 7 |
| Fungal skin infection | | | |

| | | | |
|-----------------------------|----------------|-----------------|----------------|
| subjects affected / exposed | 1 / 8 (12.50%) | 1 / 5 (20.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Gastroenteritis | | | |
| subjects affected / exposed | 3 / 8 (37.50%) | 2 / 5 (40.00%) | 1 / 3 (33.33%) |
| occurrences (all) | 5 | 2 | 3 |
| Genital infection fungal | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 1 / 5 (20.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Infection | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 1 / 5 (20.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Influenza | | | |
| subjects affected / exposed | 2 / 8 (25.00%) | 2 / 5 (40.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 2 | 2 | 0 |
| Laryngitis | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 1 / 5 (20.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Localised infection | | | |
| subjects affected / exposed | 2 / 8 (25.00%) | 2 / 5 (40.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 5 | 5 | 0 |
| Moraxella infection | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 1 / 5 (20.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Nail bed infection | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 1 / 5 (20.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Nasopharyngitis | | | |
| subjects affected / exposed | 7 / 8 (87.50%) | 5 / 5 (100.00%) | 2 / 3 (66.67%) |
| occurrences (all) | 75 | 66 | 9 |
| Oral herpes | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 1 / 5 (20.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Oral infection | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 1 / 5 (20.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Parotitis | | | |

| | | | |
|-----------------------------------|----------------|----------------|----------------|
| subjects affected / exposed | 1 / 8 (12.50%) | 1 / 5 (20.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 3 | 3 | 0 |
| Pharyngitis | | | |
| subjects affected / exposed | 2 / 8 (25.00%) | 1 / 5 (20.00%) | 1 / 3 (33.33%) |
| occurrences (all) | 2 | 1 | 1 |
| Pneumonia | | | |
| subjects affected / exposed | 2 / 8 (25.00%) | 1 / 5 (20.00%) | 1 / 3 (33.33%) |
| occurrences (all) | 3 | 2 | 1 |
| Respiratory tract infection | | | |
| subjects affected / exposed | 2 / 8 (25.00%) | 1 / 5 (20.00%) | 1 / 3 (33.33%) |
| occurrences (all) | 3 | 1 | 2 |
| Sinusitis | | | |
| subjects affected / exposed | 3 / 8 (37.50%) | 2 / 5 (40.00%) | 1 / 3 (33.33%) |
| occurrences (all) | 4 | 2 | 2 |
| Subcutaneous abscess | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 1 / 5 (20.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 4 | 4 | 0 |
| Tinea versicolour | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 1 / 5 (20.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 3 | 3 | 0 |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 2 / 8 (25.00%) | 1 / 5 (20.00%) | 1 / 3 (33.33%) |
| occurrences (all) | 5 | 1 | 4 |
| Urinary tract infection | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 5 (0.00%) | 1 / 3 (33.33%) |
| occurrences (all) | 1 | 0 | 1 |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|--|
| 13 December 2013 | This was Amendment Number 1 to Protocol Version 1.0 dated 08 April 2013. The protocol was amended to allow inclusion of 2 subjects based in Norway who had participated in the Phase 3 trial (rhLAMAN-05). It had not been possible to identify a physician and a clinical department in Norway willing to continue treatment of these subjects; the amendment allowed these subjects to continue treatment at the clinical trial site in Denmark. |
| 23 December 2013 | This was Amendment Number 2 to Protocol Version 1.0 dated 08 April 2013. The protocol was amended to allow inclusion of 1 subject based in the United Kingdom who had participated in the Phase 3 trial (rhLAMAN-05). The local hospital was reluctant to continue treatment of this subject, the amendment allowed this subject to continue treatment at the clinical trial site in Denmark. |
| 07 January 2015 | This was Amendment Number 3 to Protocol Version 1.0 dated 08 April 2013. The trial objectives were modified to include evaluation of efficacy of repeated velmanase alfa i.v. treatment of subjects and an additional CEV was added to evaluate additional efficacy parameters and safety laboratory assessments. The secondary efficacy objectives added were: evaluation of impact of long-term treatment with velmanase alfa upon serum oligosaccharides, endurance (3MSCT, 6MWT), pulmonary function, motor proficiency (Bruininks-Oseretsky Test of Motor Proficiency, 2nd edition [BOT-2]), hearing, cognitive development (Leiter International Performance Scale - Revised), central nervous system involvement (only in subjects who had participated in rhLAMAN-02 and had baseline assessments for the imaging studies), biomarkers and oligosaccharides in CSF and oligosaccharide clearance in urine and quality of life (questionnaires). Assessment of in vivo biological activity in plasma and pharmacokinetic analysis were added to secondary objectives. Additional safety assessments added at the CEV included haematology, coagulation tests, biochemistry, serum IgG/IgA/IgM, anti-nuclear antibodies, ADAs, urinalysis, 12-lead electrocardiogram and echocardiogram. Assessment of changes in social and leisure skills was also planned during the CEV. An End of Comprehensive Evaluation Visit was also added. An interim analysis of CEV data was added. |
| 20 May 2016 | In Protocol Version 2.0 dated 15 April 2016, as well as the above-mentioned amendments, the duration of the trial was extended from 3 to 6 years (and additional yearly evaluation visits included). The laboratory analysing blood samples for ADAs was updated. A Port-a-Cath could be inserted at Investigator's discretion to ease the delivery of velmanase alfa and other i.v. procedures during the trial. |
| 19 April 2017 | Protocol Version 3.0 dated 12 January 2017 reflected the change in Sponsor (from Zymenex to Chiesi) and in the name of the study treatment (from Lamazym to velmanase alfa). The primary objective (evaluating the safety of repeated velmanase alfa i.v. treatment in subjects with alpha-mannosidosis) was updated to specify that this included monitoring of the long-term safety profile, including immunogenicity (ADAs), throughout the trial. The maximum infusion duration was updated from 45 ml/hour to 22.5 ml/hour. The laboratory analysing IgG NABs in seropositive subjects was updated. A CRO (Cromsource) was appointed to submit clinical trial documentation to the relevant authorities, and to monitor the investigational sites. |
| 05 January 2018 | In Protocol Version 4.0 dated 06 June 2017, Poland was included as a second country to allow subjects based in Poland to have infusions in their country. In addition, a time window of ± 2 months was included for the yearly evaluations. |

| | |
|-----------------|--|
| 24 May 2019 | In Protocol Version 5.0 dated 05 March 2019, the duration of the trial was extended to September 2020 to ensure aftercare for subjects until velmanase alfa was available on the market. Collection of additional blood samples for research was included to develop a bioanalytical assay for the evaluation of the oligosaccharides content in the mononuclear cells. An additional evaluation visit was included to be performed before the subject left the trial. |
| 01 May 2020 | In Protocol Version 6.0 dated 26 September 2019, the duration of the trial was extended to September 2022 (and additional yearly evaluation visits included) to ensure aftercare for subjects until velmanase alfa was available on the market. The BOT-2 assessment was added at yearly evaluations (previously only at the CEV) and collection of serum oligosaccharides at dose visits every 24 weeks and yearly evaluations (previously only at the CEV). Additional laboratory tests (haematology and biochemistry pre-infusion at yearly evaluations and IgG/IgM/IgA pre-infusion at dose visits every 24 weeks) and the corresponding safety endpoint of clinical laboratory parameters was added. It was specified that an IRR was an ADR that occurred during or within 2 hours after the end of infusion of velmanase alfa (previously defined as ADRs that occurred during or after the infusion of velmanase alfa). The acceptable contraceptive methods for women of childbearing potential were specified in the exclusion criteria. The laboratories for oligosaccharide testing were updated. The hosting of the electronic data capture system was transferred to a new provider. A centre in Italy was included for infusions due to the potential inclusion of an Italian subject who had participated in the Phase 2 trial (rhLAMAN-08). Protocol Version 1.0 Italy dated 07 November 2019 was applicable only for Italy and was modified on the basis of general Version 6.0. Of note, the Italian subject was not enrolled in the trial as the subject was treated in the commercial setting. |
| 26 October 2021 | Protocol Version 7.0 dated 25 May 2021, included the possibility of permitting subjects based in Norway to have infusions in their country of living. Additional blood samples were requested to further investigate the immunological response of subjects to vaccines (poliovirus, diphtheria toxin, tetanus toxin, pneumococcal polysaccharide, and Hemophilus influenzae type b). The IgE testing process in connection with IRRs was clarified. The possibility to use the serum samples remaining after IgG antibody analyses, upon subjects' consent, for additional research was added. Yearly evaluation time windows were updated from ± 2 months to never <7 months apart (ideal interval was 12 months). The infusion rate was updated from a maximum of 22.5 ml/hour to a maximum of 25 ml/hour to align with the summary of product characteristics. Pregnancy was added as a reason for subject withdrawal, and inclusion of follow-up in case of pregnancy. The interim analysis of CEV data was deleted. The laboratory analysing IgG NABs in seropositive subjects was updated and the new database and application (Viedoc) in place was specified. The possibility to include the Italian subject from Phase 2 trial (rhLAMAN-08) was deleted as this subject would now be treated in the commercial setting. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported